Breast Cancer Risk and Environmental Exposures

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Although environmental contaminants have potential to affect breast cancer risk, explicit environmental links to this disease are limited. The most well-defined environmental risk factors are radiation exposure and alcohol ingestion. Diet is clearly related to the increased incidence of breast cancer in developed countries, but its precise role is not yet established. Recent studies have implicated exposure to organochlorines including DDT as a risk factor for breast cancer in the United States, Finland, Mexico, and Canada. Other investigations have discovered associations between breast cancer risk and exposures to chemical emissions and some occupational exposures. Several points must be considered in evaluating the relationship of environmental exposure to breast cancer. Among these considerations are the mechanism of tumorigenesis, timing of environmental exposure, and genetic modulation of exposure. Epidemiologic and ecologic investigations must take into account the very complex etiology of breast cancer and the knowledge that tumorigenesis can arise from different mechanisms. Thus crucial exposures as well as reproductive events related to breast cancer may occur years before a tumor is evident. Moreover, environmental contaminants may alter reproductive development, directly or indirectly, and thereby affect the course of tumorigenesis. Such alterations include change in gender, change in onset of puberty, and inhibition or promotion of tumor formation. Timing of exposure is therefore important with respect to mechanism and susceptibility. Finally, genetic polymorphisms exist in genes that govern capacity to metabolize environmental contaminants. Higher risk may occur among persons whose enzymes either are more active in the production of procarcinogens or fail to detoxify carcinogenic intermediates formed from chemicals in the environment. — *Environ Health Perspect* 105(Suppl 4):891–896 (1997)

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Introduction

Breast cancer is the most common malignancy among women in the United States and in western Europe. Approximately 500,000 women worldwide and 150,000 women in the United States are affected each year, yet we cannot explain its causes nor can we predict who will be diagnosed with breast cancer. The major risk factors for breast cancer are age, country of birth, and family history. Many other acknowledged risk factors can be traced to reproductive events that influence lifetime levels of hormones. A recent report identified 41 to 47% of risk to be explained by one's age at the time of first complete pregnancy, family history, and income (*1*).

Wide variations have long been noted in international incidence in breast cancer, and differences also exist between ethnic groups (*2*). In addition, breast cancer rates internationally have risen dramatically in recent years, and not all of the increase is explained by enhanced screening (*3*). These observations suggest that environmental factors play a role in one or more of the possible pathways leading to carcinogenesis. Environmental exposures can be prevented; therefore, we should pay close attention to potential environmental causes of breast cancer.

Rose et al. (*4*), among others, noted a correlation between international incidence of breast cancers and a country's average fat intake. In subsequent analytical studies, this relationship has not proved to be a strong association, although significant risks have been identified in some reports (*5*). However, a similar relationship between international incidence of colon cancer and dietary fat intake has been confirmed in subsequent studies (*2*). Moreover, certain kinds of fat may be protective: olive oil consumption, for example, has been associated with reduced risk of breast cancer (*6*). Therefore, it may be argued that the measurement of dose as fat intake requires greater precision in epidemiologic studies of breast cancer.

Likewise, our inability to quantitate exposure in studies of the environmental etiology of the disease may explain the lack of substantive evidence on environmental exposures and risk of breast cancer. Two notable exceptions exist. Evidence for risk of breast cancer from exposure to ionizing radiation is quite strong, and risk associated with alcohol intake has gained acceptance (Table 1).

Mechanistic Considerations

In the 1950s, Armitage and Doll (*7*) advanced the theory of multistage carcinogenesis, based on the observed slope of six for log-incidence versus log-age curves (Figure 1). The curves seen are similar for premenopausal breast cancer and a number of other cancers, including colon cancer. However, a marked drop in slope around

Table 1. Alcohol use and radiation exposure: known environmental risk factors for breast cancer.

Exposure	Relative risk
Alcohol (>3 drinks per day)	1.3
Radiation (atomic bomb or intense radiation therapy)	2–6

Data from John and Kelsey (*59*).

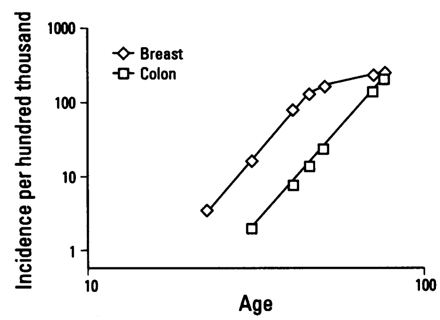

Figure 1. Age-specific incidence of breast and colon cancer per hundred thousand women, 1969 to 1971. Data from Pike et al. (*8*).

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Abbreviations used: DES, diethylstilbestrol; DMBA, dimethylbenzanthracene; DNU, dimethylnitrosourea; NAT, *N*-acetyl transferase; PAHs, polycyclic aromatic hydrocarbons; PCBs, polychlorinated biphenyls; RFLP, restriction fragment length polymorphism; TCDD, 2,3,7,8-tetrachlorodibenzodioxin.

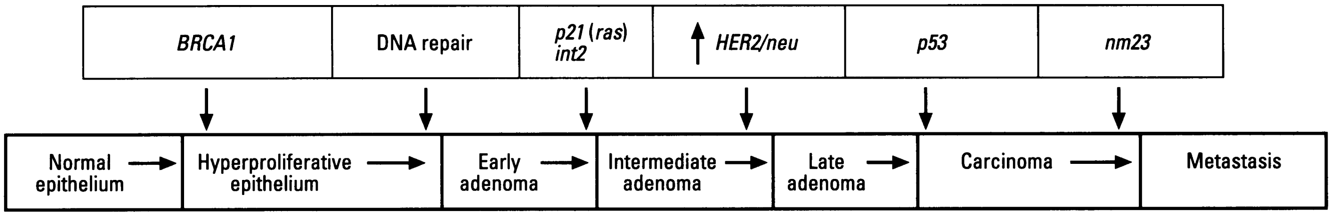

Figure 2. Proposed model of progression in multistage breast tumorigenesis. [After Vogelstein (*9*)]

age 50, corresponding to age of menopause, signifies the dramatic impact of ovarian hormones on the occurrence of breast cancer (*8*).

By analogy to Vogelstein's detailed view of colon cancer (*9*), multiple steps lead to breast cancer, beginning with initiation and followed by promotion. These changes may include mutations in oncogenes and tumor-suppressor genes (Figure 2), steps that can be induced by DNA mutations from environmental exposures. Tumor growth may be promoted by exposure to endogenous hormones or exogenous environmental hormone mimics.

Family history of breast or ovarian cancer constitutes a well-known risk factor for breast cancer. However, family history accounts for only 5 to 10% of the incidence of breast cancer (*1*). Szabo and King (*10*) consider inheritance of mutations in *BRCA1*, *BRCA2*, *p53*, ataxia telangiectasia, androgen receptor, *ras* and estrogen receptor to be important risk factors. Variants among some of these genes are thought to explain familial breast cancer risk. However, inherited mutations in these genes altogether contribute less than 15% to breast cancer risk. In addition, not all women who inherit an aberration in *BRCA1* develop breast cancer, which suggests that a gene–environment or gene–gene interaction may be responsible for its ultimate effect (*11,12*).

Other genetic factors may be more important, especially in terms of gene–environment interactions. In particular, certain enzymes have the potential to metabolize environmental agents to procarcinogens and ultimate carcinogens. These proteins are polymorphic and some variants are more or less efficient for activation or detoxification (Table 2). The prevalence of specific variants may further vary by ethnicity (Table 2), and one report has found an increased risk of breast cancer among African-American women who harbor an MsPI variant in *CYP1A1* (*13*). Additional risk may arise when specific exposures are experienced by individuals with an at-risk genotype. For example, Ambrosone et al. (*14*) have reported greatly elevated risk among women who were slow acetylators (deficient in *NAT2*) who also had a long history of heavy cigarette smoking. This is consistent with observations that persons who lack the capacity to acetylate aromatic amines are at greater risk for bladder cancer following exposure to aniline dyes (*15*).

Tumor Initiators

Chemical carcinogens may be broadly classified as initiators or promoters. Laboratory studies offer many clues to possible environmental etiology of breast cancer. *In vivo* studies show that tumors can be initiated and promoted in rodents by different classes of chemicals that represent important classes of environmental pollutants, for example polycyclic aromatic hydrocarbons PAHs and polychlorinated biphenyls PCBs. *In vitro* experiments show that chemicals in the environment can cause genetic damage, modulate cell proliferation, bind to hormone receptors, and regulate enzyme activity.

As many as 160 chemicals cause mammary tumors in rodents (16). Dimethylbenzanthracene (DMBA) and dimethylnitrosourea (DNU) are classic mammary tumor initiators in rodents. A number of these, primarily initiators that cause DNA mutations, are also well-recognized environmental contaminants: ethylene dibromide, vinyl chloride, carbon tetrachloride, dichloromethane, diethylstilbestrol (DES), estradiol, methylnitrosourea, 3-methylcholanthrene, and DMBA (*16*). However, little evidence exists to support these chemicals as breast carcinogens in humans. For solvents and PAHs, a few ecologic studies (*17–19*) and correlations with occupational exposures (*20–22*) are consistent with the experimental data; however, these observations do not provide convincing evidence linking chemical exposures to breast cancer. Our failure to find associations in humans that reflect the experimental findings may be attributed in part to our inability to adequately characterize exposure. In general, current epidemiologic methods are not able to measure exposure at the actual time of tumor initiation, which occurs 20 to 40 years before diagnosis, because most chemical agents do not persist long in the body.

Timing of Exposures

An essential characteristic of the model for mammary tumorigenesis (Figure 2) is that the time at which exposures occur is

Table 2. Allelic frequencies of some Phase I and Phase II metabolism genes.

	Frequency of minor allele				
Gene/RFLP	Caucasian	Asian	African American	Other	Reference
CYP1A1					
/MspI or Ile - val	0.10	0.33[a]	0.22	–	(*60*)
	0.11	–	0.22	–	(*13*)
CYP1A2 (phenotype)	0.41	–	–	–	(*61*)
	0.38	0.22	–	–	(*62*)
CYP2E1					(*63*)
/DraI	0.08	0.31[a]	0.09	–	(*64*)
/RsaI or /PstI	0.02	0.25[a]	0.02–0.05	–	(*65*)
GST-μ null	0.54	0.45	0.13	0.48[b]	(*66,67*)
GST-θ null	0.20	0.64[c]	0.22	0.1[d]	(*68*)
NAT2 any, null = less	0.74	0.52[a,e]	0.59	0.57[b]	(*69*)
NAT2 null	0.56	–	0.41	–	(*70*)
NAT2 slow phenotype	0.50 NS	–	–	–	(*62*)
	0.30 S	–	–	–	(*62*)
NAT2 phenotype	0.54	0.14	0.34	–	(*15*)

Abbreviations: RFLP, restriction fragment length polymorphism; GST, glutathione *S*-transferase; NS, nonsmoker; S, smoker. [a]Japanese. [b]Hispanic. [c]Korean. [d]Mexican. [e]Chinese.

important. Animal models clearly demonstrate that initiating exposures (e.g., DMBA, DNU) are most effective when they occur early in life, at a time when breast epithelium is proliferating (*23*). Similar evidence in humans is scarce, but supports the view that timing of exposures is critical. Age at reproductive milestones is widely acknowledged to be relevant to breast cancer risks; thus it is clear that early menarche, late pregnancy, and late menopause confer risk. For environmental exposures, radiation exposure at an early age (younger than 20 years) imparts a high risk of later breast cancer, while exposures among women over 40 years of age show modest increased risk (Table 3) (*24*). Similarly, cigarette smoking, which has not been an accepted risk factor for breast cancer, in some studies is associated with greater risk among women who began smoking at an early age (*25*).

Tumor Promotion and Hormonal Activity

Promotion of mammary cancer by environmental agents is suspected to occur because many of these chemicals behave *in vivo* and *in vitro* much like estrogen. Plant derivatives, pesticides, and plasticizers have been reported to mimic hormones. These compounds bind to the estrogen receptor (*26*), induce tumor-cell proliferation (*27*), and promote mammary tumor formation in rodents (*28,29*). The hallmark of estrogen response in the rodent is increased uterine weight, an effect observed with a wide range of environmental agents (Table 4).

Table 3. Radiation and breast cancer risk among atomic bomb survivors.

Age at radiation exposure years	Relative risk at dose of 1 SV
40–60	1.6
20–40	2.2
10–20	3.1
<10	4.0

Data from Tokunaga et al. (*24*).

Table 4. Effects on age at puberty and cyclicity of chemical treatment in the rat.

	Vaginal opening[a]	Acyclicity
Coumestrol	Normal: 35 versus 35 days	Premature: 83% day 135
Aroclor 1221	Early: 28 versus 42 days	Premature: 64% day 180
TCDD	Never: 80%	Irregularity

[a]Puberty. Data from Whitten et al. (*71*); Gellert (*72*); Gray and Ostby (*73*); Li et al. (*74*).

During gestation or early life, estrogenlike exposures accelerate female development. Uterine weight gain is caused by treatment with estrogen, DES, *o,p'*-DDT, coumestrol, equol, bourbon extracts, methoxychlor, chlordecone (kepone), and the following PCBs: Aroclor 1221, 1232, Aroclor 1242, Aroclor 1248, 2,2',5,5'-tetrachlorobiphenyl, 2-chlorobiphenyl, 2,2'-dichloroiphenyl,2,2',4,4',6,6'-hexachlorobiphenyl, and 4-hydroxy-2',4',6'-trichlorobiphenyl. Uterine weight loss is induced by treatment with BHC and 2,3,7,8,-tetrachlorodibenzodioxin, dioxin (TCDD) (*26,30–39*). In wildlife, feminization of alligators (*40*) has been attributed to organochlorine exposures. Experimental studies in turtles have elicited male-to-female gender alterations with exposure to PCB metabolites (*41*).

Several reports have suggested an association between exposure to DDT and breast cancer risk (*42–44*). In these studies, persistent organochlorines were determined in individual women, providing an integrated measure of long-term internal dose. Several epidemiologic studies are underway to clarify the relationship of DDT exposure to breast cancer. Observations of curtailed lactation among women with elevated DDT exposures (Figure 3) suggest that organochlorines can exert hormonal effects in humans.

In contrast, other compounds, including TCDD, are antiestrogenic (*45*) and inhibit tumor growth in rodents (*46,47*). Exposure to TCDD delays onset of puberty in female rodents and reduces uterine weight (Table 4 and above).

Though quite limited, data in humans are consistent with the antiestrogenic effects of TCDD. In young men exposed perinatally to dioxinlike PCBs and polychlorinated dibenzofurans, delayed development of male reproductive organs has been observed (*48*). Deficits of breast and uterine cancer have been seen in Seveso, Italy, during 10 years following an industrial accident that produced TCDD emissions (*49*). Other reports, however, suggest elevated breast cancer mortality among women with longer term exposure to TCDD (*50,51*). Thus it may be that short term exposure to TCDD is protective, while long-term exposure to dioxin, which is otherwise a potent animal carcinogen, enhances breast cancer risk.

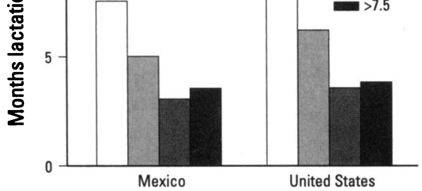

Figure 3. Duration of lactation in months according to level of DDE in breast milk lipids. Data from Gladen and Rogan (*75*) and Rogan et al. (*76*).

Experimental data on PCBs indicate that these compounds may produce either agonist or antagonist responses in hormonal systems. Both structure and relative rate of metabolism, i.e., biological half-life, control what hormonal effects may occur in humans (*52*). Structure determines receptor binding affinity, while metabolism dictates how long biological effects last in the body. Therefore, certain PCBs are estrogenic but are rapidly excreted and their effects last for only a few months after a single exposure; other PCBs (and TCDD) are antiestrogenic and have half-lives of several years. Some PCBs have estrogenic potential in animals only through their metabolites (*53*). Moreover, PCBs and other organochlorines may interact synergistically with the estrogen receptor, perhaps through multiple binding sites on this receptor (*54*).

Soy and other foods, including legumes, are rich in the isoflavone phytoestrogens (genistein, daidzein, coumestrol). These compounds have a broad range of potential anticancer effects, as estrogen agonists and antagonists, as antioxidants, by inhibiting aromatase enzymes, and by altering serum hormone building properties. Countries with diets high in soy generally have low breast cancer incidence, which has been attributed to lower levels of steroid hormones among women residing in these areas (*55*). Lower hormone levels and reduction in cancer risk may result from a combination of factors, including a high fiber, low fat, low calorie diet as well as high levels of phytoestrogens and antioxidants. In Singapore, an investigation of dietary components related to breast cancer risk suggested that high soy intake was protective and that meat intake was a risk factor (*56*).

The hormonal activity of soy constituents has been widely studied, and recent findings show that single isoflavones can be either estrogenic or antiestrogenic in different circumstances. Whether an agonist or antagonist affects results is dependent upon the dose level (high or low) and the timing of exposure. Genistein, an isoflavone found in soy products, inhibits mammary tumorigenesis in rats (*57*). Coumestrol, like antiestrogenic PCBs and TCDD, causes premature anovulation in rats, whereas an estrogenic PCB (Aroclor 1221) or DDT can hasten the onset of puberty (Table 4). Another isoflavone, zearalenone, given to mice before day 5 of age delays puberty but after day 5 causes earlier onset of puberty (*58*).

Understanding the chemical interactions and the lifelong hormonal implications of environmental exposures requires careful attention to onset, duration, and toxicokinetic characteristics of chemical agents. Mixtures normally occur in the environment such that populations are not exposed to a single chemical moiety, but interactions of chemicals in the body are not well understood. Simple additive models may approximate biological effects at one moment of exposure, but such models cannot take into account relative rates of metabolism, susceptibility due to inherited metabolic capacity, susceptibility due to breast epithelial development, or synergistic interactions of chemicals.

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